REMARKS

Claims 1-24 were rejected. Applicants have amended Claims 1-3, 5, 14, 18-20, and 22-24, and added Claim 25, to recite more clearly and distinctly that which applicants consider their invention. Support for amendment to Claim 14 and new claim 25 are found throughout the specification as filed, and particularly at page 11, line 26 to page 12, line 14.

Applicants also amended the paragraph bridging pages 18 and 19 to correct an obvious typographical error. In the relevant part of the paragraph, a PDGF/VEGF core domain or homology domain is identified. The typographical error indicated that this domain is the fragment between amino acids 230-245. The correct designation should be 230-345, which represents the C-terminal of the polypeptide, as the specification indicates (see page 7, line 27-28). In addition, the typographical error is obvious because at only 16 amino acid long, it does not contain the 8 conserved cystein residues it must contain (see page 3, lines 17-19). No issues of new matter have been raised. Entry of the claim amendments and favorable reconsideration are respectfully requested.

Claim Objections:

The objection to the claims for failing to recite in full what PDGF-C stands for has been overcome by the amendment to Claim 1.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

1. Lack of Written Description

The Office Action rejected all pending claims for alleged lack of written description. Specifically, the Office Action states that the specification as originally filed does not support a genus of nucleotide sequences encoding a PDGF-C polypeptide or an analog or a functional fragments thereof. Applicants respectfully traverse.

Applicants would like to emphasize that the claims are directed to methods for producing transgenic non-human animals that overexpress a PDGF-C polypeptide. This is significant because written-description analysis for such method claims is different from analysis for claims claiming the polypeptides or polynucleotides *per se*. In the method claims as well the claims drawn to transgenic animals and cells isolated therefrom, the DNA or protein molecules are auxiliary to the subject matter of the claim. The holding in *In re Herschler*, 591 F.2d 693, 200 USPQ 711 (CCPA 1979), is directly on point. There, the court held that a "corresponding written description [needs to be] only so specific as to lead one having ordinary skill in the art to that class of compounds." See *In re Herschler*, 591 F.2d at 697, 200 USPQ at 714 (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO). Furthermore, the court there held that "a functional recitation of those known compounds in the specification may be sufficient." *Id.* See also *In re Smythe* , 480 F.2d. 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" because the description of the properties and functions of the air or other gas segmentizing medium would suggest to person skilled in the art that appellant's invention includes the use of "inert fluid" broadly.)

In the instant case, the claims similarly recite a class of known compounds (see *e.g.* Li *et al.*, 2000, Nature Cell Biology 2:202-309 (copy attached) and references cited therein, which describes the active core domain of PDGF-C and histidine tagged PDGF-C constructs (p303 second column) and the plasmin-generated core domain of 28K (p305)), and the specification provides a detailed description of the biochemical and functional characteristics, see page 7, line 16 to page 9, line 20. In addition, the specification provides an adequate number of representative species for the recited "genus" of polypeptides, thereby satisfying the written description requirement even if the analysis is under the standard when the polypeptides are the claimed subject matter. Specifically, applicants direct the Examiner's attention to exemplified polypeptides on page 8, lines 15-

20, page 19, lines 5-9, page 23, lines 15-20 (for human c-myc epitope tagged PDGF-C, and cDNAs coding for PDGF-C peptides, and PDGF-C encoding polynucleotides with a promoter tagged to it), Example 1 (with polyadenalation sequence tag), Example 4 (processed intermediates of PDGF-C).

Furthermore, to clarify that a distinct class of molecules is recited, applicants have amended the claims to recite that the polypeptide is either a PDGF-C, or an analog or a fragment thereof having a PDGF-C activity. These recitations, examples and amendments are sufficient to lead one of ordinary skill in the art to that class of compounds, namely any polypeptide molecules having PDGF-C activities. Accordingly, the rejection for alleged lack of written description is improper and should be withdrawn.

2. Lack of Enablement

The Office Action further rejected all pending claims for alleged lack of enablement. The reasons asserted for the rejection may be summarized as (1) an alleged lack of adequate written description for the genus of PDGF-C polypeptides; (2) transformation of cells and embryogenesis was only exemplified with the mouse; (3) even for mouse transformation, the use of cells for transformation and embryogenesis are not exemplified other than ES cells or pronuclei; (4) it is unpredictable whether sufficient level and specificity of gene expression may be obtained if different promoters or different cell types are used. Applicants traverse the rejection and refute the above reasoning below.

The improper nature of the lack-of-written-description rejection with regard to PDGF-C polypeptides has been discussed above. Therefore it is no longer relevant to the enablement analysis. Applicants note, however, that because the Office Action appears to mix improperly written description analysis with enablement analysis, an improper conclusion was reached.

With regard to the asserted unpredictability and difficulties in producing transgenic animals other than the mouse, applicants note that as of the filing date of the instant application, numerous successful examples had been reported

that produced transgenic animals in animal models other than the mouse. In fact, the paragraph in Polejaeva *et al.* quoted by the Office Action starts with a sentence that "[t]ransgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep, cattle and goats." There is no reason known to applicants or articulated in the Office Action that still more successful examples cannot be produced. It may be true that producing transgenic animals is a difficult, time-consuming and perhaps unpredictable process, but this cannot be equated with "undue experimentation," the legal standard under which lack of enablement should be analyzed. This only shows that the art typically engages in this type of complex experiments. It is well established that complex experimentation is not necessarily undue experimentation, especially if the art typically engages in such experimentation. *See* e.g. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Office Action discusses the fact that ES technology is generally limited to the mouse system, and from there concludes that only claims limited to transgenic mice are enabled.

The emphasis on the success of the ES approach in mice, however, is misplaced. Other approaches have been successful in many other animal models. Polejaeva *et al.* itself states in the introduction that even though ES technology does not yet exist in many farm animal species, the development of somatic cell nuclear transfer has bypassed the need for livestock ES cells. Pro-nuclear microinjection has been used to make transgenic animals other than mice and this had been done prior to the filing date of the instant application. Polejaeva *et al.* on page 119 at the end of the paragraph entitled pronculcar injection describes the production of transgenic sheep using somatic cell nuclear transfer (*citing* references 43), and the paragraph entitled "Gene targeting in live stock cells" on page 121 describes other examples. Rulicke *et al.* clearly stated that in the abstracts that direct injection of transgene into the pronucleus of a fertilized oocyte has been used successfully for the past 15 years. Therefore the problems raised by the examiner have solutions already in the state of the art at the time of filing. The Office Action misquoted the last sentence of the

paragraph on page 119. Polejaeva *et al.* does not state that "undue experimentation" is needed. It merely stated that the experimentation may be complex due to the mosaic nature of the first generation transgenic animal.

The Office Action further states that it would require undue experimentation to determine if a DNA sequence encoding the PDGF-C polypeptide is inserted at the correct site and is expressed at a level sufficient to produce a phenotype in any other transgenic non-human mammal. On page 12-13 of the Office Action discusses the unpredictability of transgene expression in different animal species.

This again is an indication of both an improper legal standard being applied and a mischaracterization of the state of the art. As of the filing date of the instant application, it was nothing more than mere routine experimentation for an ordinarily skilled person in the art to test cells taken from an animal to look for raised protein levels on an SDS-PAGE gel. It would also be very simple and straight forward to look at the integration site by sequencing DNA using primers to a known sequence. The discussion regarding perceived complexity in transgene expression level and the citation to Wall and Houdebine are improper as these references describe the state of the art in 1996 and 1994 respectively (not 1997 as stated by the examiner) and the technology had advanced dramatically since then. As of the 2001 filing date of the instant application, an ordinarily skilled artisan would be able to screen and obtain the desired transgene expression specificity and expression level by routine methods well known in the art. For example, methods for determining the location of the integrated DNA are provided by Mullins on page 1558 at the beginning of the first column, and methods for improving efficiency of generating transgenes are provided by Wall on page 62.

With regard to the phenotypes that may be expressed in a claimed transgenic animal, the Office Action asserts that only the exemplified promoter and phenotype is enabled. However, many "off-the-shelf" type promoters are known and readily available (see e.g. page 11, lines 11-16 of the specification for

other tissue-specific promoters), and incorporating promoters other than the alpha myosin promoter with a polynucleotide encoding a PDGF-C polypeptide to express the polypeptide in different tissues only requires routine experimentation by an ordinarily skilled person in the art. Similarly, the skilled artisan can then test the effect of PDGF-C antagonists in tissues other than the heart. Accordingly, applicants respectfully submit that the present claims are fully enabled.

With regard to page 15 of the Office Action relating to Claim 1, applicants have amended Claim 1 to recite the transgenic DNA comprising a suitable promoter. Similarly, Claims 20-21 have been amended to recite that the monitoring step is performed in vitro with an isolated cell from the transgenic animal.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Applicants have amended claims 2, 3, 20 and 22-24, thereby overcoming the rejections of these claims for alleged indefiniteness.

The rejection of Claims 10-17 for alleged indefiniteness is respectfully traversed. Applicants respectfully submit that there is no basis in the law or in the custom that a dependent claim must start with a "the" rather than a "a." A survey of the issued U.S. patent claims will reveal that both are acceptable even though some practitioners prefer one over the other. Inasmuch as parent Claim 9 embraces any number of animals, it is proper to use the indefinite article "a" or "an" to indicate that the dependent claims are directed to any one of these animals, whereas the use of the definite article "the" may imporperly imply that the parent claim embraces only a single animal. Withdrawal of this rejection is respectfully requested.

In summary, Applicants respectfully submit that all claims are now in condition for allowance. If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be

appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #1064/48487).

Respectfully submitted,

March 20, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph bridging pages 18 and 19 has been amended as follows:

Transgenic DNA refers to DNA that is introduced into a cell so that the DNA is incorporated into the genome of the cell. The cell may be capable of giving rise to a transgenic animal which contains the transgenic DNA. Generally, the transgenic DNA for administration into a particular cell can be constructed using a transgenic vector. A preferred DNA is a polynucleotide that encodes for full-length PDGF-C or an analog thereof, and a more preferred DNA is that which encodes for the activated truncated PDGF-C or an analog thereof. The truncated portion of PDGF-C comprises at least a portion of the PDGF/VEGF homology domain (P/VHD) of PDGF-C. The minimal sequence is residues [~~230-245~~] 230-345 of SEQ ID NO:1. However, the domain can extend towards the N terminus up to residue 164 of SEQ ID NO:1. Herein the P/VDH of PDGF-C is defined as truncated PDGF-C. The truncated PDGF-C is an activated form of PDGF-C.

IN THE CLAIMS:

Claims 1-3, 5, 14, 18-20 and 22-24 have been amended as follows:

1. (Amended) A method for producing a transgenic, non-human animal overexpressing a polypeptide having platelet-derived growth factor C (PDGF-C) activity [~~PDGF-C~~] or an analog [~~thereof,~~] or a functional fragment [~~of~~] having a PDGF-C activity [~~or an analog thereof~~], the method comprising the steps of:

a) introducing a transgenic DNA into a cell of a non-human animal, said transgenic DNA comprising a polynucleotide sequence operably linked to a suitable promoter, said polynucleotide encoding [~~for~~] a polypeptide having PDGF-C activity, [~~PDGF-C~~] or an analog [~~thereof,~~] or a functional fragment [~~of~~] having a PDGF-C activity [~~or an analog thereof~~];

b) allowing said transgenic DNA to integrate into said cell;

c) introducing said cell from step b) into a non-human animal; and

d) allowing said cell from step c) to develop into a transgenic, non-human animal.

2. (Amended) The method of claim 1, wherein said cell of step a) is [~~the~~] a pronuclei of a fertilized oocyte and said introducing of step c) is implanting said fertilized oocyte into a pseudopregnant non-human animal.

3. (Amended) The method of claim 1, wherein said cell of step a) is an embryonic stem cell; said integrating of step b) is integrating said DNA into [~~the~~] a genomic DNA of said embryonic stem cell; and said introducing of step c) is introducing said embryonic stem cell into a developing embryo.

5. (Amended) The method of claim 4, wherein said promoter is selected from the group consisting of[:] alpha-myosin heavy chain promoter, keratin K14 promoter, and insulin promoter.

14. (Amended) A transgenic, non-human animal according to Claim 9, wherein the animal is homozygous with regard to the transgenic DNA [~~that is a descendant from an animal according to claim 11~~].

18. (Amended) A fertilized oocyte containing transgenic DNA that encodes [~~for~~] a polypeptide having PDGF-C activity, [~~PDGF-C~~] or an analog [~~thereof,~~] or a functional fragment [~~of~~] having a PDGF-C activity [~~or an analog thereof~~].

19. (Amended) An embryonic stem cell containing transgenic DNA that encodes [~~for~~] a polypeptide having PDGF-C activity, [~~PDGF-C~~] or an analog [~~thereof,~~] or a functional fragment [~~of~~] having a PDGF-C activity [~~or an analog thereof~~].

20. (Amended) A method for identifying a compound as a PDGF-C antagonist, said method comprising the steps of:

introducing said compound into a transgenic, non-human animal overexpressing a polypeptide having PDGF-C activity, [~~PDGF-C~~] or an analog [~~thereof,~~] or a functional fragment [~~of~~] having a PDGF-C activity [~~or an analog thereof~~];

monitoring [~~the~~] in vitro a biological activity of PDGF-C in an isolated cell from said animal; and

identifying said compound as a PDGF-C antagonist where PDGF-C biological activity is inhibited.

22. (Amended) A method for identifying a compound as a PDGF-C antagonist, said method comprising the steps of:

[~~introducing said compound into~~] exposing to said compound a cell isolated from a transgenic, non-human animal overexpressing a polypeptide having PDGF-C activity or an analog or a functional fragment thereof having a PDGF-C activity;

assaying [~~the~~] an effect of said compound on said cell; and

identifying said compound as a PDGF-C antagonist where the PDGF-C biological activity of said cell is altered.

23. (Amended) A method of screening a compound for inhibition of hypertrophy, comprising the steps of:

administering a pharmaceutically active amount of said compound to a transgenic, non-human animal overexpressing a polypeptide having PDGF-C activity or an analog [~~thereof, or a functional fragment of PDGF-C or an analog thereof~~] or a fragment thereof having PDGF-C activity; and

monitoring [~~the~~] cardiac development of said animal;

determining said compound inhibits hypertrophy where said cardiac development is [~~normal~~] inhibited when compared to a control transgenic, non-human animal in the absence of said compound.

24. (Amended) A method of screening a compound for inhibition of fibrosis, comprising the steps of:

administering a pharmaceutically active amount of said compound to a transgenic, non-human animal overexpressing a polypeptide having PDGF-C activity or an analog [~~thereof, or a functional fragment of PDGF-C or an analog thereof~~] or a fragment thereof having PDGF-C activity; and

monitoring the cardiac development of said animal;

determining said compound inhibits fibrosis where said cardiac development is [~~normal~~] inhibited when compared to a non-treated control transgenic, non-human animal.